Surgical Adjuvant Chemotherapy in Cancer of the Breast:

Results of a Decade of Cooperative Investigation

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(and Cooperating Investigators)

IN 1957, under the auspices of the National Institutes of Health, Cancer Chemotherapy National Service Center, representatives of 23 institutions (Table 1) adopted a common protocol which was to determine the efficacy of administering chemotherapy in conjunction with "curative" cancer surgery to decrease recurrence and extend survival of patients with cancer of the breast. The impetus and rationale for this undertaking resulted primarily from laboratory observations[2, 9, 10] relative to favorable effects of chemotherapeutic agents on disseminated tumor cells in experimental animals, as well as reports of the frequent presence of cancer cells in the circulating blood of patients with tumor.[4, 5] Thio-TEPA (Triethylenethiophosphoramide), because of its effectiveness in palliation of mammary cancer, was at that time deemed the drug most likely to be beneficial and was chosen for evaluation. The first patient was entered in this study on April 4, 1958, and patient entry was terminated October 7, 1961. Preliminary reports of data collected as of March 1961 and November 1962 have been published.[11, 12] This paper primarily presents detailed information relative to the influence of treatment on recurrence, survival, postoperative complications, and other pertinent findings in 826 acceptable patients entered in the Surgical Adjuvant Breast Cancer Study, designated as Phase I, who have completed 5 years of follow-up study.

Upon completion of patient entry into Phase I, a new study, Phase II, was begun to evaluate 5-Fluorouracil (5-FU), compared to Thio-TEPA, as an adjunct to radical mastectomy and to determine the value of postoperative radiotherapy and prophylactic oophorectomy in treating mammary cancer. Moreover, it was hoped that confirmation or denial of the effects of Thio-TEPA being observed in Phase I, would be forthcoming. Many of the institutions contributing to Phase I continued to participate in the new protocol. Some withdrew; others have been added (Table 1). Thirty-six institutions were or are actively

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TABLE 1. *Distribution of Patients in Phase I and Institutions Participating in Evaluation of TSPA as an Adjunct to Surgery for Breast Cancer (Phases I and II)*

Hospital or University	Principal Investigator	Patients Entered Phase I	Percentage of Total Phase I
Alabama	Champ Lyons, M.D.	20	2.4
Baylor	Michael E. DeBakey, M.D.	8	1.0
Boston	Henry M. Lemon, M.D.	2	0.2
Cornell*	John M. Beal, M.D. George N. Cornell, M.D.*	55	6.7
Duke*	William W. Shingleton, M.D.	38	4.6
Emory*	John D. Martin, Jr., M.D.	10	1.2
George Washington	T. Crandall Alford, M.D.	22	2.7
Hahnemann	John M. Howard, M.D.	68	8.2
Kings County*	Irving Enquist, M.D. Bernard Gardner, M.D.*	76	9.2
Louisville*	Rudolf J. Noer, M.D.	26	3.1
Marquette*	John Hurley, M.D. Edwin H. Ellison, M.D.*	28	3.4
Maryland	Arlie E. Mansberger, Jr., M.D.	22	2.7
Med. Coll. of Evangelists*	Clarence E. Stafford, M.D.	28	3.4
Mississippi	James D. Hardy, M.D.	9	1.1
Nebraska*	Daniel M. Miller, M.D.	40	4.8
Pennsylvania*	Robert G. Ravdin, M.D.	73	8.8
Pittsburgh*	Bernard Fisher, M.D.	59	7.1
Roswell Park*	Thomas L. Dao, M.D.	79	9.6
Temple*	George P. Rosemond, M.D.	88	10.7
UCLA	Donald B. Rochlin, M.D.	9	1.1
Vanderbilt	William Scott, Jr., M.D.	5	0.6
Wayne State*	Henry J. VandenBerg, Jr., M.D.	38	4.6
Wisconsin*	Anthony R. Curreri, M.D.	23	2.8

* Also participant in Phase II.

Additional Participants—Phase II

Albany	Charles Eckert, M.D.	Memorial Hosp.	Joseph H. Farrow, M.D.
Albert Einstein	Herbert Volk, M.D.	Miami	Daniel S. Martin, M.D.
Am. Oncologic Hosp.	Joseph G. Strawitz, M.D.	Michael Reese Hosp.	Gerald Peskin, M.D.
California	Leon Goldman, M.D.	Ohio State	Neil C. Andrews, M.D.
Cincinnati	William Altemeier, M.D.	Oregon	William W. Krippaehne, M.D.
Graduate Hosp.	William S. Blakemore, M.D.	Penrose Cancer Hosp.	John Karabin, M.D.
Harbor General Hosp.	James C. Thompson, M.D.	Puerto Rico	Luis A. Vallecillo, M.D.
Iowa	R. T. Tidrick, M.D.	Southern California	Lewis W. Guiss, M.D.
Johns Hopkins	Edward F. Lewison, M.D.	St. Luke's Hosp.	Harold A. Zintel, M.D.
Louisiana State	Isidore Cohn, Jr., M.D.	St. Vincent's Hosp.	Louis M. Rousselot, M.D.
McGill	John D. Palmer, M.D.	Tulane	Edward T. Krementz, M.D.

engaged in Phase II. The first patient was entered into the second study on November 9, 1961. As of January 8, 1968, there were 1,341 patients who had received Thio-TEPA, Placebo, or 5-FU and who had been followed for at least 18 months.

This paper presents therefore, in addition to a complete report of Phase I, a Progress Report which is primarily concerned with tumor recurrence rates in these 1,341 patients. Data relative to postoperative radiotherapy and prophylactic oophorectomy will be the subject of a separate report.

Procedure—Phase I

The participating groups in this study were surgical services of universities or cancer institutes. Contribution of patients by each was not equal, since it depended primarily upon the extent of available material (Table 1). Half of the institutions entered 28 or more patients. A detailed ex-

planation of organization of the study and protocol employed has been presented in the previous reports [11, 12] and will be summarized in the following.

Patient Distribution and Entry

The experimental design of this study consisted of two options—treatment with conventional Halsted radical mastectomy and Thio-TEPA (TSPA) and radical mastectomy with Placebo (control). Initially, option selection was determined by a "blind envelope" technic and no placebo was given. Subsequently, and for most of the study, the traditional "double-blind" method was employed. This change was made to provide the greatest reliability in reporting post-surgical complications and related patient observations. With institution of the complete "double-blind" system, each patient scheduled for, or undergoing radical mastectomy was registered by direct telephone contact with the statistical center. A treatment assignment was made from a coded series of vials which had been labeled in the statistical unit prior to being supplied to participating investigators. Selection of either TSPA or Placebo was from a previously prepared randomization in the statistical unit. In emergency, when subsequent treatment of the patient depended upon knowledge of the agent used, a "code break" was available. This occurred 15 times—six in the placebo group and in nine of those receiving TSPA. Seven of the latter were because of leukopenia or depression of platelet counts. One patient receiving Placebo also experienced a leukopenia.

Initially TSPA patients received 0.8 mg./Kg. of body weight of this drug, 0.4 mg./Kg. given at time of operation and 0.2 mg./Kg. on each of the first two postoperative days (105 patients, Part I terminated October 15, 1958). As a result of the many complications reported from other adjuvant studies using the same drug and dosage, the total amount of drug administered was reduced to 0.6 mg./Kg. Patients were administered 0.2 mg./Kg. the day of operation and on each of the subsequent 2 days (636 patients, Part II terminated April 1, 1961). Since it was later demonstrated in this study that complications were minimal and equal in the two Parts, it was deemed advisable to revert to the original dosage schedule until the termination of patient entry (85 patients, Part III). An analysis of data has revealed no differences in any of the Parts. Consequently, unless otherwise stated, results are presented for all Parts combined.

Patients were considered eligible for inclusion only if (1) the tumor was con-

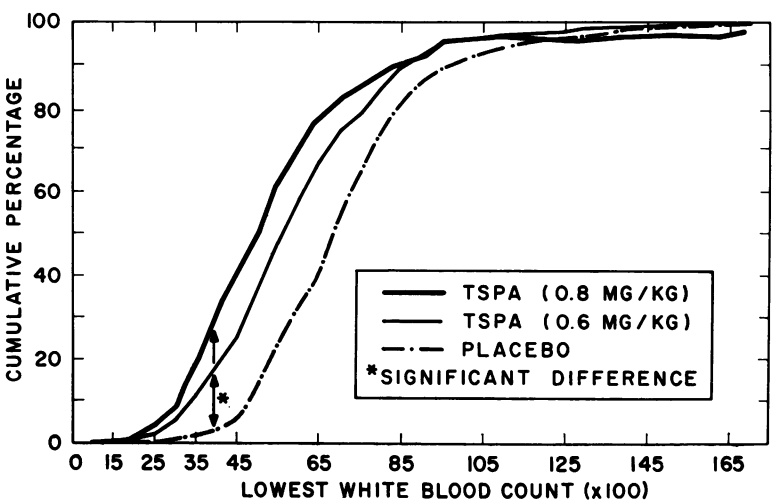

FIG. 1. Lowest white counts during first postoperative month for TSPA and Placebo.

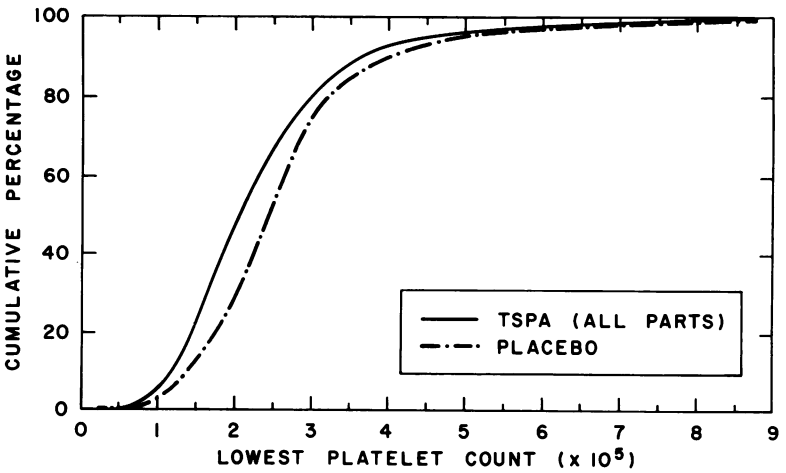

FIG. 2. Lowest platelet counts during first postoperative month (counts weekly).

fined to the breast or breast and axilla; (2) the tumor was movable in relation to the chest wall without extensive skin involvement or ulceration; (3) axillary nodes, if present, were movable in relation to chest wall and blood vessels and there was no evidence of edema of the arm; (4) there was histologic evidence of malignancy; (5) a Halsted radical mastectomy, removing breast, pectoral muscles and axillary contents en bloc had been performed; (6) age was between 30 and 70 years.

Patients were excluded from the study because of (1) previous or concomitant malignancy regardless of site, except squamous and basal cell cancers of the skin; (2) previous treatment of mammary cancer other than performance of a biopsy to confirm diagnosis no more than 7 days prior to definitive surgery; (3) preoperative WBC $< 5{,}000$ and/or platelet counts $< 150{,}000$; (4) being a poor "surgical risk"; (5) breast tumors other than carcinoma or the presence of extensive subepidermal skin involvement (inflammatory carcinoma); (6) pregnancy or lactation.

Of 1,465 patients registered with the statistical unit during the 2½-year period, 826 were found to be acceptable for study. Patients were excluded for the above reasons (Type #1 exclusions) or because of serious breach in protocol (Type #2 exclusions), such as failure to administer the proper amount of drug at the prescribed time. Less than one-third of those discarded were of the latter type (Table 2). The large number of Type #1 exclusions was due to the fact that all patients with breast lesions were registered with the statistical center upon admission to hospital and prior to complete evaluation relative to acceptability.

Recurrence and survival data were compiled from 820 patients rather than the 826 since, despite all efforts, nodal status of six patients was unobtainable. Three of the six, all postmenopausal, received TSPA. Four of the six have survived without evidence of recurrence beyond 5 years, one has been tumor-free for 4 years, and one who received TSPA died 6 months following surgery of disseminated metastases.

In this study patients were categorized as pre- or postmenopausal from the menstrual history.

Data Collection

To collect, coordinate and collate data and to prepare reports, a statistical unit was formed at Roswell Park Memorial Institute in Buffalo, New York. This agency continues to function as a repository for patient information. Information regarding all entries, from the time of initial contact and entry in the study through the continuation of follow-up, was reported to the statistical

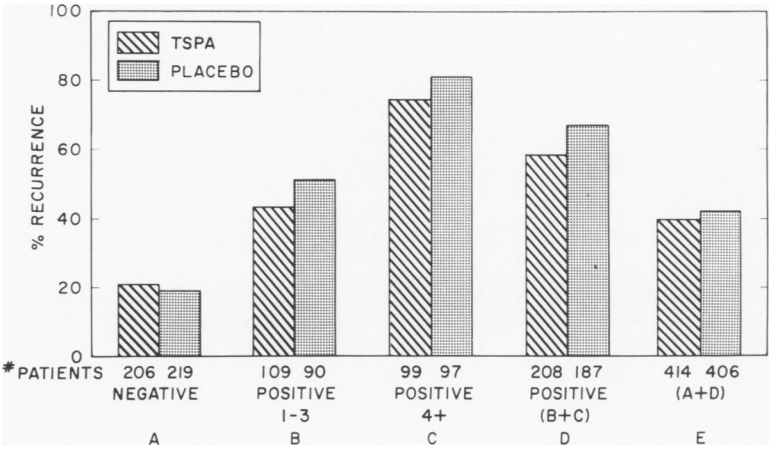

FIG. 3. Recurrence rates in patients grouped according to nodal status.

unit on standard forms. As patient data accumulated, it became obvious that machine supported procedures would be necessary to handle the material. A data storage and retrieval methodology was developed to absorb the complete set of forms in machine readable language. Subsequently, programs were prepared to review and edit the input data and alert the statistical unit staff of certain logical contradictions, omissions, and other difficulties in the patient chart. The entire chart was then subjected to a technical review by research analysts and final review by a staff physician. Correspondence with the responsible investigator was initiated and continued until all matters in question were resolved.

Follow-Up

At the onset of this study each patient was seen by a physician at the participating institution or by her own physician every 3 months following operation. Relaxation of this time schedule was subsequently effected to permit phone contact of patients on alternate quarters. All contacts were recorded and reported to the statistical unit on appropriate forms. Chest x-rays were performed semiannually and appropriate investigations were carried out when recurrences were suspected. Biopsies were done when possible. No treatment was prescribed by the protocol for recurrences. Each was handled by the investigator as deemed proper. When proof of recurrence could not be obtained because of its location or other pertinent reason, the opinion of the attending physician was accepted. Time of recurrence was recorded as that time after operation when confirmatory evidence was obtained or a definite judgment of its presence was made and reported. The method of contact employed when recurrence was established was recorded (Table 3). Seventy-nine per cent of recurrences were diagnosed at the hospital where primary treatment was carried out and an additional 19 per cent was found either at another hospital or in a doctor's office. Thus, in this study a recurrence is defined as a satisfactorily proven metastasis following radical mastectomy.

In this report of 826 patients a follow-up study loss, relative to survival, was 1.2 per cent at 48 months and 5.5 per cent at 60 months. A critical examination was made of follow-up study frequency. To obtain this percentage the actual number of forms received for a patient was divided by the theoretical number which should have been submitted (one for every 3 months on the study). Frequently the actual number exceeded the theoretical number. As a result of examination of this data it may be stated that (1) there was no evidence that adequancy of follow-up studies differed for

TABLE 2. *Reasons for Patient Exclusion (Phase I)*

Patients Registered	1,465	
Patients Unacceptable	639	
Exclusions Type #1		445
Exclusions Type #2		194
Acceptable study patients	826	

Patient Class	Type of Therapy Given: No Therapy Given	TSPA	Control	Therapy Given (Code Break Unknown)	Total
Acceptable	—	417	409	—	826
Unacceptable					
Type #1*	391	22	23	9	445
Type #2**	79	42	66	7	194
Total	470	481	498	16	1,465

* Type #1 exclusions include benign lesions, previous cancer, poor surgical risk, widespread metastasis, pregnant or lactating, previous cancer therapy, low blood count, inflammatory disease, non-resectable tumors, or male.
** Type #2 exclusions include all breaches of the protocol serious enough to have a possible influence on the results.

treatment of control groups; (2) patients with recurrences tended to have a greater number of visits relative to the theoretical number than did patients without recurrences; (3) postmenopausal patients (particularly those with 4+ positive nodes) had a higher per cent of follow-up examinations than premenopausal patients; and (4) follow-up visits appeared adequate in that their number was in keeping with the prescribed number for the time-on-study.

Methods of Analysis

Since all patients have had the opportunity to be studied for 60 months—the time of follow-up study in this report—and since follow-up study loss was minimal, direct recurrence and survival rate calculations * were employed rather than the life table methods used in the earlier reports. Results obtained with this method of calculation were compared with those obtained utilizing crude death rates, the life table method of Cutler and Ederer,[3] of an adjusted death rate. They were similar for each, fully justifying utilization of the method employed in this study. Differences between TSPA and Placebo recurrence and survival rates were tested by the Chi-Square test (Yates corrected) and differences between distribution of months to recurrence were evaluated by the Wilcoxon test.[1]

In this report the use of the phrase "statistically significant" means that the result would be highly unlikely (e.g., occur no more than 5% of the time) if there was no real difference between the groups compared.

* Direct recurrence or death rate = $\frac{\text{Recurrences or deaths in 5 yrs.}}{\text{Patients followed 5 yrs.}}$

Procedure—Phase II

The conditions of the protocol and ancillary information presented for the Phase I study are, with few exceptions, the same for Phase II. In this study patients were arbitrarily defined as premenopausal if they were 30 through 49 years of age and postmenopausal if age 50 or over. The TSPA was administered just as in Parts I and III of Phase I. All patients received a total dose of 0.8 mg./Kg. Those getting 5-FU received 15 mg./Kg. intravenously on each of 4 successive days beginning on postoperative day 7 for a total of 60 mg./Kg. In one premenopausal option (A) and in one postmenopausal option (D), patients

selected at random received either TSPA or 5-FU in equal numbers. In premenopausal options B (radiotherapy) and C (oophorectomy) control patients were selected at random in a double-blind fashion so as to receive either TSPA or Placebo. This was similarly carried out in postmenopausal radiotherapy options E and F. In comparing results of Phase II with Phase I, those options (B and C) of Phase II in which TSPA was given at random with Placebo were combined since they differed only with respect to the third treatment (radiotherapy or oophorectomy) which was not involved in comparison with Phase I results.

Results—Phase I

A. Complications and Mortality

Local Complications (Table 4). Tabulation of the incidence and type of local complications revealed no statistically significant difference between those receiving TSPA or Placebo. Approximately one-third of the patients in either group had some undesirable local surgical complication. It is emphasized that there were no differences in such sequelae between patients receiving 0.8 mg./Kg. TSPA and those getting 0.6 mg./Kg. TSPA.

First Systemic Complications (Table 5). The first systemic complications recorded in both treated and control groups were varied and, for the most part, were typical of what might be encountered following any major operative procedure, i.e., fever, nausea, pyelonephritis, atelectasis or pneumonia, psychosis, etc. There were, however, three treated patients who developed aplastic anemia. All were entered into the study at its inception (Part I). Subsequently this complication was not encounted. All three developed severe wound complications. One died between the first and second postoperative month with death attributed to arteriosclerotic heart disease. The remaining two are alive and well. It was noted that thrombophlebitis

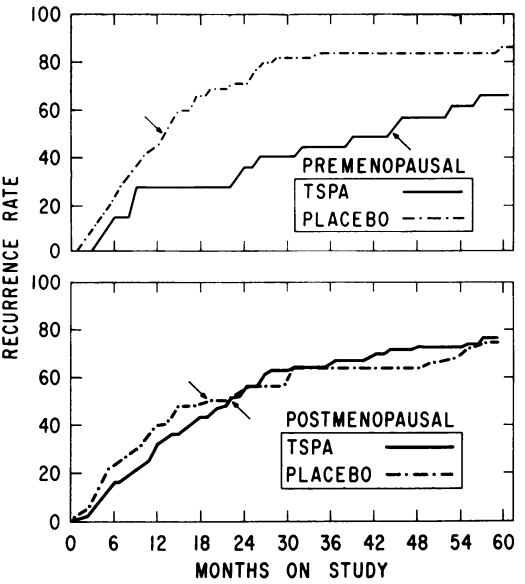

FIG. 4. Recurrence rates up to 60 months of follow-up for patients with four or more positive nodes. (Arrows indicate time of 50 per cent of recurrences.)

accounted for nine of the 37 complications occurring in the Placebo group, whereas this was not encountered in those receiving TSPA. More severe complications, such as vena caval thrombosis, renal failure, perforated ulcer and pulmonary embolism were encountered, for the most part, as single instances and were distributed between the two groups. There were fewer patients with systemic complications in the TSPA group than in control patients.

Distribution of the lowest white blood counts recorded during the first postoperative month (counts made weekly) revealed a difference between those receiving TSPA and a Placebo (Fig. 1). Whereas almost 20 per cent of the former had counts less than 4,000, in only 2 to 3 per cent of the latter group did this occur. The percentage of patients with depressed white counts ($<$ 4,000) was significantly greater (30%) following administration of 0.8 mg./Kg. of TSPA than after 0.6 mg./Kg. (17%). Platelet count depression was not as pronounced (Fig. 2). Only 2 to 3 per cent of all patients studied had a platelet count below 100,000.

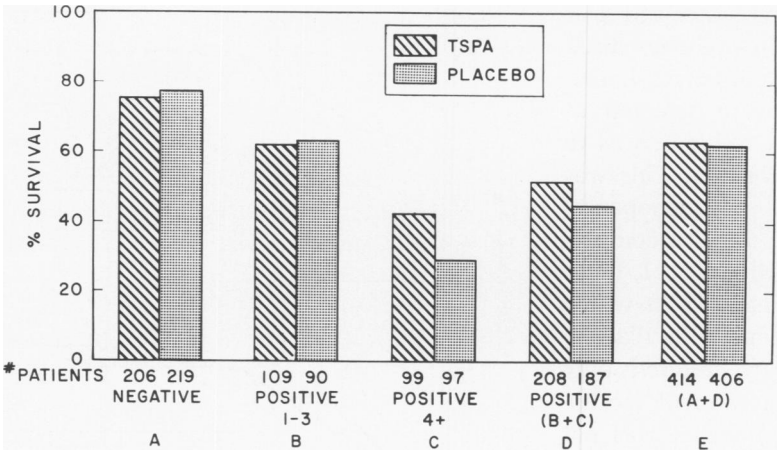

FIG. 5. Survival rates at 5 years of follow-up for TSPA and Placebo according to nodal status.

Postoperative Mortality. There were two deaths occurring within 30 days of operation. Both were in patients receiving Placebo. One was attributed to renal failure with subsequent pulmonary edema and congestion. The second was the result of massive pulmonary embolus.

B. Tumor Recurrence

Recurrence Rates. When menopausal status was disregarded, examination of data at the end of 5 years (Fig. 3) revealed no appreciable difference between treated and untreated patients in any nodal category. There was a recurrence rate of 20 per cent in all patients with negative nodes and a 62 per cent recurrence in such patients having any number of positive lymph nodes. Analysis of the data relative to the number of tumor-containing axillary nodes revealed a distinct difference between those with 1–3 and those with four or more nodes involved. All of those with only 1–3 positive nodes had a significantly less recurrence rate (47%) than did those with 4+ nodal involvement (77%). The recurrence rate for all patients entered in this study was 40 per cent for those receiving TSPA and 42 per cent for those given Placebo.

Recurrence data was then grouped according to nodal and menopausal status of patients. Five years of follow-up (Table 6) revealed no significant difference in recurrence rate between patients receiving TSPA or Placebo in any of the six principal categories (relative to nodal and menopausal status). While there appeared to be a slightly lower recurrence rate in premenopausal patients with 4+ positive nodes and in postmenopausal patients with 1–3 positive nodes who had received TSPA, the difference did not approach statistical significance. Considerable overlap of confidence limits occurred in each category.

Data reviewed only at the end of 5 years of follow-up study failed to reveal all significant information relative to tumor recurrence. Distribution of recurrence rates for TSPA and Placebo groups up to 60 months, similar to a plot of life table values, demonstrated no significant difference between the two at any time in five of the six categories. This is exemplified by a plot of recurrence rates for postmenopausal patients with 4+ positive nodes up to 60 months of follow-up study (Fig. 4). A similar plot for premenopausal patients with four or more positive nodes revealed, however, a difference in the TSPA and Placebo groups (Fig. 4) which was greatest (approximately 40%) between the eighteenth and thirty-sixth postoperative months. Subsequently, increased numbers of recurrences in TSPA treated patients gradually lessened the difference so that by 48 months the dissimilarity had dimin-

ished to below the level of statistical significance for groups of this size. The effect of TSPA in this category is best demonstrated by the observation that 50 per cent of the patients in the Placebo series had recurrences by 13 months after operation, whereas recurrences in half of the TSPA treated patients did not occur until the forty-fifth month of follow-up study. Among all patients in this category the median postoperative month to recurrence was 12 months for those receiving Placebo and 24 months following TSPA therapy.

Recurrence Site (Table 7). Approximately one-third of all first recurrences (31%) were reported to be in the integumentary system. Forty-eight per cent of these were in the skin of the chest wall or axilla and 37 per cent were found in the operative scar. The remaining 15 per cent were distributed to such sites as supraclavicular, submandibular, shoulder and eyelid skin. No significant differences in incidence in this system were observed in TSPA or Placebo treated patients, either premenopausal or postmenopausal, with or without positive nodes.

Twenty-six per cent of all recurrences were found in the skeletal system. Almost all bones were represented in the list of those with metastases. A greater predilection for ribs and spine was evident. Fourteen (17%) of the 80 recurrences in bone were in the former and 32 (40%) in the latter. While neither menopausal status nor nodal involvement influenced the incidence of recurrence in this system, it was of interest to note that more of the recurrences in this system were in treated (TSPA) than in untreated patients (59% versus 41%).

One-fifth of all first recurrences were found in the respiratory system. The percentage in this location was less in premenopausal than postmenopausal women. Recurrences were also observed in axillary, supraclavicular, hilar, cervical and other lymph nodes, as well as in liver, stomach, ovaries and brain.

C. Survival

Survival Data. Survival data, just as that for tumor recurrence, was grouped into six categories according to nodal and menopausal status of patients. Five years of follow-up study (Table 8) demonstrated that at that time the survival rates for TSPA and Placebo groups were not appreciably different except in the premenopausal patients with 4+ positive nodes. In that group there was a 33 per cent difference (statis-

TABLE 3. *Methods of Contact Recorded When Recurrence was Established** (*Phase I*)

	TSPA					Placebo				
	1[a]	2	3	4	5	1	2	3	4	5
Premenopausal										
Negative Nodes	10	1	2	—	—	7	2	2	—	—
1–3 Positive Nodes	10	1	1	—	—	10	3	1	—	1
4+ Positive Nodes	17	—	1	—	—	23	2	4	—	2
Postmenopausal										
Negative Nodes	20	4	—	—	—	19	3	3	—	—
1–3 Positive Nodes	19	4	2	—	1	26	—	3	1	—
4+ Positive Nodes	41	5	3	—	1	30	3	5	2	1
Total	117	15	9		2	115	13	18	3	4

* Includes recurrences occurring beyond 60 months.

[a] Methods of contact are: 1=original hospital, 2=other hospital, 3=M.D.'s office, 4=telephone, 5=other.

TABLE 4. *Incidence of Local Complications (Phase I)*

	TSPA		Placebo	
	#	%	#	%
Patients entered	417	—	409	—
Patients with complications	147	35	133	33
Total incidence of complications	191	—	168	—
Type of complications:				
Hematoma/Seroma	61	32	41	24
Wound infection	42	22	36	21
Wound dehiscence	12	6	12	7
Necrosis (major)	20	10	19	11
Necrosis (minor)	47	25	50	30
Loss of skin graft	9	5	10	6

TABLE 5. *First Systemic Complications (Phase I)*

	TSPA	Placebo	Total
# Patients	417	409	826
# with complications	22	37	59
% with complications	5.3*	9.0	7.1

* Significantly different from control ($P < 0.05$).

TABLE 6. *Effect of TSPA or Placebo with Radical Mastectomy on Recurrence at 5 Years Post Treatment (Phase I)*

	Premenopausal		Postmenopausal	
	TSPA	Placebo	TSPA	Placebo
Negative Nodes				
N—Total patients	55	54	151	165
L—Lost to follow-up*	4	7	31	29
R—Recurrences	12	11	23	24
%R—Percent Recurrence	24	23	19	18
1–3 Positive Nodes				
N	21	24	88	66
L	1	1	17	9
R	11	11	28	30
%R	55	48	39	53
4+ Positive Nodes				
N	23	37	76	60
L	0	1	11	8
R	15	31	49	40
%R	65	86	75	77

* Relative to recurrence information.

tically significant) in survival rate in favor of those who received TSPA. Moreover, whereas 50 per cent of the Placebo treated patients in the group were dead by approximately 20 months, more than 50 per cent of those receiving TSPA were still alive at 60 months. This finding reflects the difference observed in recurrence. Since patients survive for a period of time following discovery of a metastasis, the dissimilar survival might be expected to become apparent at a later follow-up time. Whereas the inequality in survival rates did not reach a level of statistical significance until 30 months of follow-up study, that for recurrence rates occurred at 18 months. The 5-year survival was 58 per cent for all premenopausal patients and 65 per cent for those postmenopausal.

When menopausal status was disregarded and patients were grouped according to nodal status (Fig. 5), a difference between the TSPA and Placebo groups was only evident in those with 4+ positive nodes. There was a 5-year survival rate of 76 per cent for all patients, treated or untreated, with negative nodes, and a 49 per cent survival in such patients having any number of positive lymph nodes. Those with 1–3 positive lymph nodes had a significantly greater survival (62%) than did those with 4+ positive nodes. In the latter, those receiving Placebo had a 29 per cent 5-year survival, whereas there was a 40 per cent survival when TSPA had been administered. The overall survival of patients in this study was 63 per cent for those receiving TSPA and 62 per cent when a Placebo was administered.

To obtain a picture of the entire 5-year experience, plots of survival rates were made according to menopausal and nodal status. Those for pre- and postmenopausal patients with negative nodes were practically identical. Curves (not presented) from the TSPA and Placebo groups were almost superimposed on each other. Survival rate distribution for premenopausal patients with 1–3 positive nodes (Fig. 6A)

TABLE 7. *System of First Recurrence (Phase I). Per Cent of Total Recurrences by Therapy, Menopausal and Nodal Status (305 Patients)**

System of Recurrence	Total # Recurrences	% in All Patients Treated and Control	All Patients T[a]	All Patients C[b]	Pre-menopausal T	Pre-menopausal C	Post-menopausal T	Post-menopausal C	Negative Nodes T	Negative Nodes C	Positive Nodes T	Positive Nodes C
Integumentary	95	31	29	33	38	38	25	30	27	30	30	34
Skeletal	80	26	32	21	31	22	32	21	38	24	30	20
Respiratory	57	19	18	19	10	13	21	23	19	27	18	17
Lymphatic	40	13	11	15	10	15	11	15	5	8	14	17
Digestive	26	9	7	10	8	9	11	11	8	11	6	10
Urogenital (ovaries)	3	1	1	1	0	2	1	0	0	0	2	<1
Nervous (brain)	4	1	1	1	3	2	<1	<1	3	0	<1	2

* Includes all patients in this study with recurrences, including those occurring after 5 years.
[a] TSPA treated.
[b] Control.

was similar to that for postmenopausal patients with similar node involvement (Fig. 6B). In both, TSPA and Placebo plots demonstrated no significant difference. When data from patients with four or more positive nodes were plotted, the difference between premenopausal patients receiving TSPA or Placebo was readily appreciated (Fig. 6A). This difference did not occur in the postmenopausal group (Fig. 6B).

Cause of Death. It was of interest to analyze the cause listed for the 288 deaths which occurred during the 5-year period. Sixty-nine per cent of those who died had metastatic carcinoma. The majority of the deaths occurring in premenopausal patients (84%) was attributed to cancer. For postmenopausal patients a lower proportion (54%), especially in negative node patients (35%) was ascribed to metastatic disease. Seventy-one per cent of postmenopausal patients with 4+ positive nodes were recorded as dying of cancer. When patients were grouped according to nodal involvement with disregard for menopausal status (Fig. 7) it was observed that the percentage of deaths resulting from causes other than cancer remained constant (approximately 12%) in each of the three nodal groups. Consequently, when death rates were adjusted to denote only those patients dying with cancer, it was revealed that only 12 per cent of women found to have negative nodes at time of radical mastectomy succumbed to cancer in the subsequent 5 years. If there were 1–3 positive nodes present, 26 per cent died of cancer during that time, and when 4+ nodes contained tumor, death of 55 per cent of the women was attributable to tumor. No significant difference in the proportion of deaths due to cancer and to other causes was evident in TSPA or Placebo groups, whatever their nodal status.

Of the 31 per cent of deaths recorded as not being due to cancer, cardiovascular disease, i.e., myocardial infarction, cerebral thrombosis, etc., was most prominent. Deaths were attributed to such diverse causes as suicide, pneumonia, hepatic failure (no metastases), dermatomyositis, etc.

Recurrence to Death Intervals. Time intervals between tumor recurrence and death of patients were determined. These were evaluated with regard to therapy, menopausal and nodal status. While the time interval was similar in postmenopausal patients in any nodal status group, whether TSPA or Placebo had been administered (Fig. 8), the results in premenopausal patients were different. Curves for the TSPA and Placebo groups in each nodal status were similar to the combined plot (Fig. 8). While differences within nodal status groups were not significant because

TABLE 8. *Effect of TSPA or Placebo with Radical Mastectomy on 5-Year Survival (Phase I)*

	Premenopausal		Postmenopausal	
	TSPA	Placebo	TSPA	Placebo
Negative Nodes				
N—Total patients	55	54	151	165
L—Lost to follow-up	5	7	11	6
D—Deaths	10	9	37	38
%S—Percent survival[a]	80	81	74	76
1–3 Positive Nodes				
N	21	24	88	66
L	1	0	5	2
D	7	8	32	25
%S	65	67	61	61
4+Positive Nodes				
N	23	37	76	60
L	0	0	1	6
D	10	28	47	37
%S	57*	24	37	32

* TSPA and Placebo groups are significantly different ($P<0.05$).

[a] $\%S = \dfrac{\text{Number of patients alive}}{\text{Total patients–patients lost to follow-up}} \times 100 = \dfrac{N-L-D}{N-L} \times 100.$

of the small sample size, when all premenopausal groups were combined the Placebo patients had a significantly shorter recurrence to death interval than did those patients who received TSPA (Wilcoxon test). The median interval for the Placebo group was 6 months, whereas it was 14 months for those treated. When intervals between tumor recurrence and death were grouped according to the time from operation to recurrence (Fig. 9), it was noted that the rapidity of a tumor recurrence following operation had little influence upon the length of subsequent patient survival. Those patients whose recurrences occurred less than one year following operation had a subsequent survival time essentially similar to that for patients whose recurrences became manifest 4.1–5.0 years after radical mastectomy.

Results—Phase II

A comparison of tumor recurrence rates at 18 months following treatment with either TSPA or administration of Placebo was made between patients in Phase I and Phase II. There was a similarity in findings in most instances (Table 9). In the Phase II study, just as in Phase I, the only difference of note between the treated and untreated patients when nodal and menopausal status were considered was in premenopausal patients with positive nodes. Those patients, when treated with TSPA, again as in Phase I demonstrated a lower incidence of tumor recurrence. However, whereas in Phase I the difference in recurrence rates between all positive node TSPA treated and Placebo administered patients was highly significant (21% versus 43%), in Phase II the difference, while present, was less impressive (34% versus 50%). Examination of results (Fig. 10) obtained by using the double-blind system and the selection of patients at random with 4+ positive nodes—the group in Phase I where the greatest advantage from TSPA was obtained—revealed a difference of 38 per cent between those treated and untreated in Phase I, and only 21 per cent in Phase II. The latter difference (21%) was not statistically significant, there being considerable overlap of confidence limits for the two groups (i.e., treated and Placebo). It was of interest to note that the recurrence rate of the nondouble-blind TSPA treated patients in Phase II was only a little different (47%) than that of the double-blind group (40%).

The tumor recurrence rate at 18 and 36 months following administration of 5-FU was essentially the same as that which was observed for those patients in Phase I and Phase II who received Placebo, and showed no improvement over those patients receiving TSPA in either menopausal or nodal category (Table 10). In fact, recurrence rates in patients with positive nodes administered 5-FU were slightly greater than

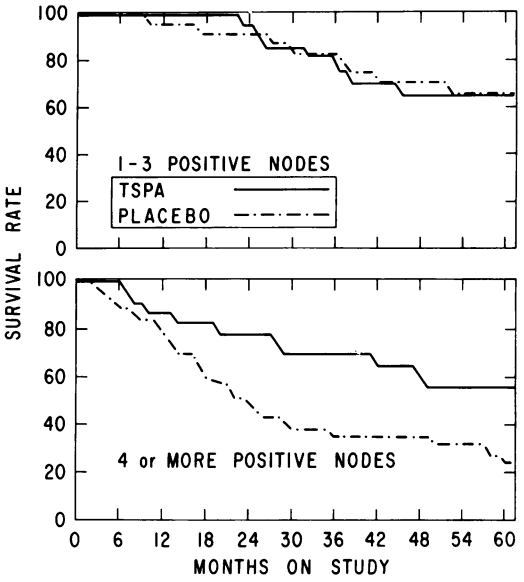

FIG. 6A. Survival rates for 5 years of follow-up for *premenopausal* patients receiving TSPA or Placebo.

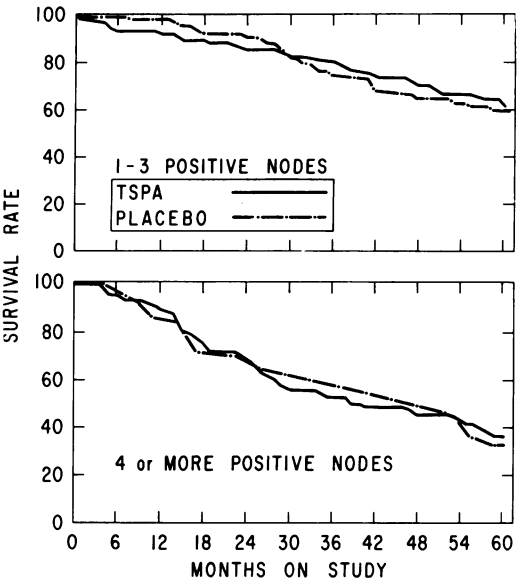

FIG. 6B. Survival rates for 5 years of follow-up for *postmenopausal* patients receiving TSPA or Placebo.

they were in those patients receiving TSPA or Placebo. The greatest difference was observed in those patients with 4+ positive nodes. The recurrence rate for those 4+ positive node patients receiving TSPA (pre- and postmenopausal combined) was 36.4 per cent, and for those administered 5-FU it was 54.4 per cent—a significant difference in favor of TSPA. The apparent improvement observed in negative node patients treated with 5-FU was not significant.

Discussion

The Halsted radical mastectomy, first described in 1894,[8] is a local form of therapy for mammary cancer which, by itself, can cure only those patients whose tumor is confined to the tissues of the chest wall and axilla removed at surgery. Observation in this study of a 5-year recurrence rate of 20 per cent in patients with negative nodes and close to 70 per cent in those with positive nodes emphasizes the inability of conventional radical surgery to eradicate all cancer cells because of their dissemination prior to or at the time of operation. More extensive regional dissection, carried to the limit of feasibility and sensibility, has not produced a substantial improvement in results. The advantage of irradiation, another form of regional therapy, as an adjunct to surgery remains to be proven. Appraisal of its worth is another phase of the Adjuvant Program, and results with this modality will be reported subsequently.

It would seem that until cancer of the breast can be prevented or a therapy becomes available which is capable by nonsurgical means of destroying both primary and secondary tumors, systemic therapy as an adjunct to surgery affords the most likely means for escape from the plateau on which the prognosis and salvage rate of this disease has been ensnared for the last 30 or more years. Logic would dictate that until a greater curability of "curable" mammary cancer can be effected, hope for such an accomplishment in advanced cancer remains remote.

These considerations prompted the reported studies. It was hoped that by the use of adjuvant chemotherapy, cells dislodged

TABLE 9. *Comparison of Recurrence Rates in Phases I and II 18 Months After TSPA or Placebo*

	Phase I				Phase II			
	TSPA		Placebo		TSPA		Placebo	
	#	%R	#	%R	#	%R	#	%R
Premenopausal patients								
Negative nodes	54	4	54	11	83	8	31	6
Positive nodes	43	21	60	43	101	34	32	50
1–3 (D/B)*	20	15	24	13	15	33	9	22
(Non D/B)					30	13		
4+ (D/B)	23	26	36	64	20	40	23	61
(Non D/B)					36	47		
Postmenopausal patients								
Negative nodes	142	5	158	4	270	4	63	8
Positive nodes	155	25	124	31	230	25	81	22
All negative node patients	196	5	212	6	353	5	94	7
All positive node patients	198	24	184	35	331	27	113	30
All patients	394	14	396	19	684	12	207	20

* D/B means double-blind.

into the blood and lymph during surgical manipulation could be eliminated.

Failure (except in one sub-group) of the two chemotherapeutic agents (TSPA or 5-FU) administered at the time of and/or shortly after surgery, in a maximum dose compatible with patient safety, to reduce the tumor recurrence rate or enhance survival does not repudiate the concept of systemic adjuvant therapy. Knowledge and hypotheses accrued since the advent of this investigation suggests that, at least in part, the original considerations upon which this study was based may have resulted from over-simplification of the biologic complexities associated with such a therapeutic regimen. Information relative to cell cycling time and the possibility that (a) cells are drug sensitive during only part of their mitotic cycle; (b) therapeutic success may be equally or more dependent upon destruction of occult metastases than upon "free" cells in the circulation; (c) the per cent reduction of neoplastic cells for a given treatment is constant regardless of the number of cells present; (d) host immunologic factors may be involved, has assumed importance in this regard.[7] From these considerations has arisen the concept of prolonged adjuvant therapy utilizing either a single or combination of chemotherapeutic agents. Phase III of the Breast Adjuvant Program will evaluate the worth of such a regimen. Only if many clinical trials cast in differing detail as a result of new knowledge prove unrewarding will a searching reappraisal of the concept of adjuvant chemotherapy be in order. These studies have demonstrated that it is possible to collect a substantial number of patients treated in a prescribed manner from a large number of institutions. Aside from providing patients more rapidly than could be acquired by a single investigator or multiple investigators working at one institution, they, as Schneiderman[13] has pointed out, have advantages over single institutional trials in that they contain within themselves a basis for internal verification. "A diversity of trials in a diversity of places at different times . . . is possibly the strongest evidence one can see of the worth of a treatment before it is employed on the whole population."[13]

While the therapeutic results obtained have not been dramatic, experience achieved with these cooperative trials should provide direction in the planning

of better protocols in the future. There can be little question that "the clinical trial is convincing in proportion to how well it has been designed." [13]

Several shortcomings of the protocols employed became apparent as the studies progressed. Observation that at 5 years only 12 per cent of all deaths of patients with negative nodes could be attributed to cancer emphasizes the impropriety of including such patients in future clinical trials. The number necessary to prove with certainty the efficacy of any treatment is not feasible short of several decades of case entry. Consequently, it is planned that future adjuvant studies will utilize only positive node ("poor-risk") patients so that a significant therapeutic response may more readily be ascertained. The inclusion of too many options and treatment groups in Phase II proved to be cumbersome. The need for a simple protocol which selects patients at random between only one test series and one control so as to answer one clearly specified question at a time is mandatory. Other procedures result in extension of the period of patient entry necessary to obtain an answer and subsequently lead to diminished enthusiasm or participating investigators with potential study deterioration. Careful statistical analysis of data obtained from these studies indicates that, based on 18-month recurrence rates, adequate test of one agent with another could be accomplished in 3½ years by utilizing only positive node patients. A 2-year intake, 200 in each treatment series, would be necessary. Preliminary evaluation of results would be available after 2½ years. Subsequent protocols of the Breast Adjuvant Therapy Program will employ this format.

It is important to emphasize that one of the advantages which this study has over other breast cancer series to be found in the literature is that treatment groups were selected at random. Consequently, the combining of subseries, such as was done with

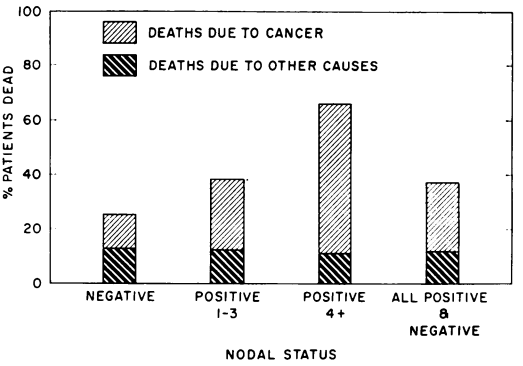

FIG. 7. Causes of deaths in patients with breast cancer followed for 5 years.

TSPA treated patients and with those receiving Placebo in Phase II to make a comparison with Phase I data was carried out with caution. For subseries to be combinable results should show a similar relationship between the treatments employed. This was found to have occurred. The recurrence rates for premenopausal patients with positive nodes treated with TSPA were consistently lower than for the recipients of Placebo. Of most concern and interest was comparison of the findings obtained from the premenopausal patients with 4+ positive nodes in Phases I and II, since this was the group in Phase I which demonstrated the effectiveness of TSPA. The similarity of the Placebo series in the two studies indicated that the results were, indeed, comparable. Failure to observe as great an effect by TSPA in Phase II as in Phase I suggests that perhaps the TSPA series in the latter study contained an unusually favorable group of patients (or there was an unfavorable population in Phase II), in which case the difference observed might not be completely attributable to the effect of the drug. Consistent presence of an advantage for TSPA treated patients in the two studies, however, offers evidence that there is some beneficial effect from TSPA in premenopausal patients with four or more positive nodes.

Speculation as to the mechanism of this salutary effect has led to consideration of

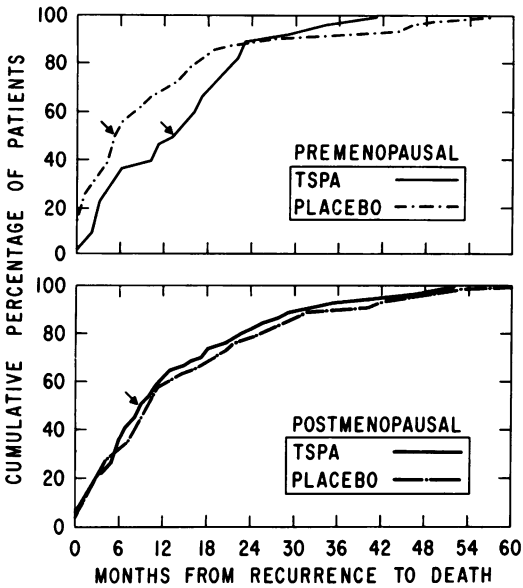

FIG. 8. Distributions of months from recurrence to death for patients treated with TSPA or Placebo regardless of nodal status. (Arrows indicate time of 50 per cent of recurrences.)

the effect of TSPA on ovarian activity. The possibility that this agent was affecting ovarian function, either by production of medical castration or by altering endocrine interrelationships, was considered. Evidence obtained from the experimental animal [6] relative to the uptake of P^{32}-labeled TSPA provides indirect support of this concept. Clinical confirmation was sought from retrospective information obtained from patients in the TSPA and Placebo groups of Phase I concerning menstrual activity following operation. Such data revealed that TSPA did influence menstrual function in the older of the premenopausal patients (> 42 years of age). Menstruation ceased in 18 of 46 patients receiving TSPA, whereas this occurred only once in 37 patients in the control group—a significant difference. There was, however, no indication that the recurrence rate was influenced by the cessation of menstrual activity.

Information regarding menstrual function following operation has been obtained routinely in the second breast study. Menstrual alteration, as determined by (a) less than six periods in the first 6 postoperative months and (b) any change in activity noted by the patient has been recorded. As in Phase I, TSPA decreased menstrual function in older patients, but evidence to relate changes to recurrence of disease was lacking.

Although 5-FU is capable, as is TSPA, of promoting regression of metastases in some patients with advanced breast cancer, this agent was for the most part less, and never more, effective than TSPA in the prevention of tumor recurrence. In addition, its use resulted in a higher rate of local, systemic and hemic complications than observed with other adjuvant therapy. The toxic manifestations of this agent are the subject of a separate report now in preparation.

Since the degree of patient toxicity encountered with this drug was considerable

TABLE 10. *Recurrence Rates 18 and 36 Months Following Surgery in Patients Receiving TSPA, Placebo and 5-FU (Phase II)*

Menopausal, Nodal and Treatment Status	18 Mo. # Patients	18 Mo. RR %	36 Mo. # Patients	36 Mo. RR %
Premenopausal				
Negative Nodes				
TSPA	83	8	57	16
Placebo	31	6	23	17
5-FU	56	4	42	14
Positive Nodes				
TSPA	101	34	88	61
Placebo	32	50	28	61
5-FU	60	43	49	61
Postmenopausal				
Negative Nodes				
TSPA	270	4	193	12
Placebo	63	8	38	16
5-FU	196	2	135	14
Positive Nodes				
TSPA	230	25	175	50
Placebo	81	22	62	50
5-FU	138	35	111	55

* RR % = % recurrence.

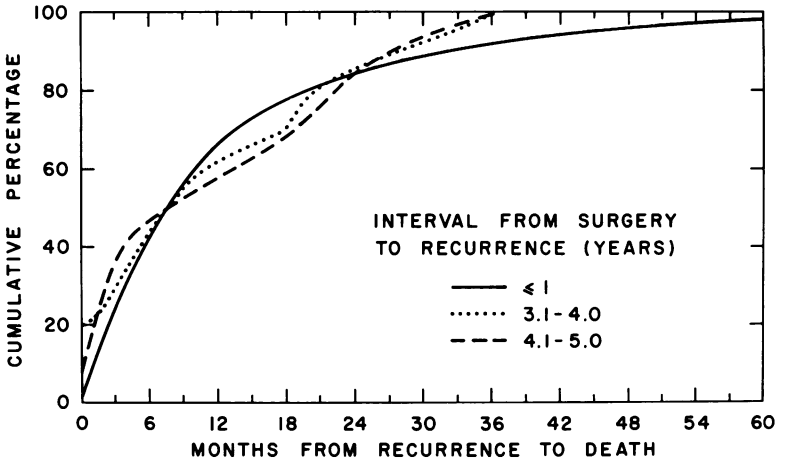

FIG. 9. Recurrence to death intervals grouped according to interval from surgery to recurrence.

and its therapeutic effect as evidenced by tumor recurrence rates 18 and 36 months after surgery was negligible, its further use as an adjuvant to breast surgery seems unjustified. Follow-up of patients who have received 5-FU will be continued, but it seems highly unlikely that any advantage from its use will be demonstrated.

Observation that survival following discovery of a recurrence was of the same duration, whether metastases appeared shortly or many years after radical mastectomy, is of interest. The occurrence of such a phenomenon would indicate that in the slower appearing tumors an acceleration of growth rate must have taken place in the course of development. That alteration of immunologic or other host-tumor relationships could be responsible are speculative and worthy of further consideration.

Prognosis of cancer of the breast has been related to the presence or absence of axillary nodal involvement rather than to the *number* of nodes demonstrating tumor. When sufficient data had accumulated in the Phase I study, a plot of numbers of nodes containing tumor in a surgical specimen versus the 24-month postoperative recurrence rate was carried out. In this preliminary examination it was observed that while a progressive increase in recurrence rate accompanied the presence of more positive nodes a sharp rise occurred with the involvement of approximately four nodes. Consequently, patients with positive lymph nodes were grouped into those with 1–3 or 4+ involvement in subsequent analysis of data. The validity of such grouping was confirmed by the observance of a 25 per cent difference in 5-year survival of patients in the two groups. These findings afford a possible explanation for differences in recurrence and survival rates in different reported retrospective nonrandomized series. The positive node patient population in one study may differ from that of another with respect to the number of involved nodes. Consequently, interpretation of data without such information may be difficult.

Summary and Conclusions

Clinical trials were begun in 1957 to evaluate the worth of chemotherapy as an adjuvant to standard radical mastectomy in the treatment of "curable" cancer of the breast. In Phase I, patients from 23 institutions were selected at random in "double-blind" fashion so that they received either Thio-TEPA (Triethylenethiophosphoramide or TSPA) or a Placebo the day of and 2 successive days after operation. Patient entry terminated in 1961. This report presents detailed information relative to the influence of such treatment on postoperative complications, recurrence, survival and

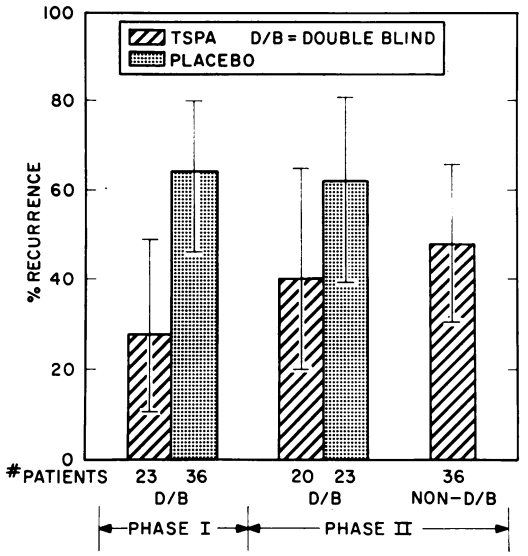

FIG. 10. Eighteen-month recurrence rates in premenopausal 4+ positive node patients—Phases I & II.

other pertinent findings obtained from 826 patients who have been studied for 5 years.

Analysis of data from the Phase I study revealed the following:

(1) One-third of all patients had one or more local surgical complication(s). No difference in incidence or type was observed between those receiving TSPA or Placebo. There were fewer systemic complications in the TSPA group than in control patients. Two deaths occurred within 30 days of operation. Both patients had received Placebo.

(2) The recurrence rate at 5 years for all patients entered in this study was 40 per cent for those receiving TSPA and 42 per cent for those given Placebo. When menopausal status was disregarded no significant difference was found between treated and untreated patients in any nodal category. Twenty per cent of those with negative nodes had a recurrence, as did 62 per cent of those with any number of positive nodes. Analysis of these data relative to *number* of axillary nodes involved revealed an important finding. Those patients with 1–3 positive nodes had a recurrence rate of 47 per cent, whereas 77 per cent of those with four or more nodes involved demonstrated recurrence. When data were grouped according to nodal *and* menopausal status of patients, 5 years of follow-up study revealed no significant difference in recurrence rates between patients receiving TSPA or Placebo in any of the six principal categories.

Distribution of recurrence rates similar to a life table plot showed, however, that TSPA had a beneficial effect in premenopausal patients with four or more positive nodes. In this sub-group, by 12 months after operation 50 per cent of the patients receiving Placebo demonstrated tumor recurrence. Half of those treated with TSPA did not recur until the forty-fourth month. The greatest difference in recurrence rate was observed between the eighteenth and thirty-sixth postoperative months. After that time, the difference gradually diminished so that by the sixtieth month it was no longer significant.

(3) A detailed analysis of the reported site of first recurrence is presented. The integumentary system (31%) was the most frequently involved, followed closely by the skeletal system (26%).

(4) Five-year survival rates for TSPA and Placebo groups in all categories, or combination of categories, were not statistically different with the exception of premenopausal patients having four or more positive nodes. In that sub-group the survival rate, reflecting the difference in recurrence, was more than twice as great for the TSPA series (57%) as for the Placebo series (24%).

(5) Cause of the 288 deaths which occurred during the 5-year period was analyzed. The percentage of deaths from causes other than cancer was approximately 12% in each of the three nodal groups. Adjustment of death rates to denote only those patients dying with cancer revealed that only 12% of women with negative nodes succumbed to cancer in the subsequent 5

years; 26 per cent died during that time when there were 1–3 positive nodes present, and deaths of 55 per cent of women with 4+ nodes were attributable to tumor. No significant difference in the proportion of deaths due to cancer and to other causes was evident in TSPA or Placebo groups, whatever their nodal status.

(6) Time intervals between notation of tumor recurrence and death of patients were recorded. Premenopausal patients receiving Placebo demonstrated a significantly shorter recurrence to death interval than did those receiving TSPA.

The rapidity of tumor recurrence following operation failed to influence subsequent length of survival.

With completion of patient intake in Phase I, a new study, Phase II, was begun to evaluate the worth of 5-Fluorouracil (5-FU) compared to TSPA as an adjunct to surgery and to confirm or deny the effects of TSPA being observed in the Phase I study.

Data from 1,341 patients receiving TSPA, Placebo, or 5-FU and who had been studied for at least 18 months, revealed the following:

(1) As in Phase I, a difference of note between TSPA treated and untreated patients in Phase II was observed in the double-blind system, selecting at random, premenopausal patients with four or more positive nodes. Whereas in Phase I at 18 months after operation there was a 38 per cent difference in recurrence rate, in Phase II this difference was less impressive, being only 21 per cent.

The constant advantage for TSPA treated patients in the two studies, however, emphasizes that there is some beneficial effect from TSPA in premenopausal patients with four or more positive nodes. Its use in others is *not* justified.

(2) Speculation as to the mechanism of this salutary effect led to an evaluation of the effect of TSPA on ovarian activity. From retrospective information obtained in Phase I and routinely collected information in Phase II, it was concluded that while TSPA affects menstrual activity in older premenopausal patients, there is no correlation between recurrence rates and alteration of menstruation.

(3) As a result of its severe toxicity and its lack of therapeutic effect, further use of 5-FU as an adjuvant to breast surgery in the regimen employed is unwarranted.

It is emphasized that (a) these findings in no way repudiate the concept of systemic adjuvant chemotherapy in the treatment of cancer of the breast; (b) future protocols and cooperative endeavors will be better as a result of the lessons learned in these studies; and (c) while controlled trials, such as those reported and contemplated, may not be the only means available for the attainment of scientific proof relative to the merits of therapy, they are by far more convincing than the retrospective, solo methods of the past.

Addendum

Administration of National Surgical Adjuvant Breast Project

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John Pickren, M.D.

Bibliography

1. Bross, I. D. J.: Is There an Increased Risk? Fed. Proc., 13:815, 1954.
2. Cruz, E. P., McDonald, G. O. and Cole, W. H.: Prophylactic Treatment of Cancer; the Use of Chemotherapeutic Agents to Prevent Tumor Metastasis. Surgery, 40:291, 1956.
3. Cutler, S. J. and Ederer, F.: Maximum Utilization of the Life Table Method in Analyzing Survival. J. Chronic Dis., 8:699, 1958.
4. Engel, H. C.: Cancer Cells in the Circulating Blood. Acta Chir. Scand., 1955 (Supp. 201).
5. Fisher, E. R. and Turnbull, R. B., Jr.: The Cytologic Demonstration and Significance of Tumor Cells in the Mesenteric Venous Blood in Patients with Colorectal Carcinoma. Surg. Gynec. Obstet., 100:102, 1955.
6. Fletcher, W. S., Dennis, D. L. and Ross, H. B.: Distribution and Possible Mechanisms of Action of Thio-TEPA in Experimental Breast Cancer. Cancer, 18:1437, 1965.
7. Frei, E., III: Selected Considerations Regarding Chemotherapy as Adjuvant in Cancer Treatment. Cancer Chemotherapy Reports, 50:1–8, 1966.
8. Halsted, W. S.: Results of Operations for the Cure of Cancer of the Breast Performed at Johns Hopkins Hospital from June, 1889–January, 1894. Ann. Surg., 20:497, 1894.
9. McDonald, G. O., Cruz, E. P. and Cole, W. H.: The Effect of Cancer Inhibitor Drugs on the "Take" of Walker Carcinosarcoma 256 in Rats. Surg. Forum, 7:486, 1956.
10. McDonald, G. O., Livingston, C., Boyles, C. F. and Cole, W. H.: The Prophylactic Treatment of Malignant Disease, with Nitrogen Mustard and Triethylenethiophosphoramide (Thio-TEPA). Ann. Surg., 145:624, 1957.
11. Noer, R. J.: Thio-TEPA with Radical Mastectomy in the Treatment of Breast Cancer. Amer. J. Surg., 106:405, 1963.
12. Noer, R. J., Chairman Surgical Adjuvant Chemotherapy Breast Group. Breast Adjuvant Chemotherapy: Effectiveness of Thio-TEPA (Triethylenethiophosphoramide) as Adjuvant to Radical Mastectomy for Breast Cancer. Ann. Surg., 154:629, 1961.
13. Schneiderman, M. A.: The Value of Controlled Trials in Clinical Evaluation in Breast Cancer. Hayward and Bulbrook, London, Academic Press, 1966, pp. 249–255.

Discussion

Dr. R. Kennedy Gilchrist (Chicago): I certainly enjoyed both of these papers, particularly, the last. I would like to ask a question—how many nodes were examined per specimen? In our laboratory a good many years ago, Dr. Munroe using the same method we developed for clearing specimens of the bowel, examined a hundred patients operated upon by several surgeons performing radical mastectomy for cure. When the average number of nodes per specimen was more than 28, patients with no nodes involved had no recurrence of cancer within 5 years.

The number of nodes in these specimens varied anywhere from 45 to 16. The surgeon who averaged 16 preached radiation and simple mastectomy to all of his patients, and his cure rate was very low, even in those with no nodes involved. I might say we arrived at the same figure presented here; when less than four nodes were involved, the cure rate was very good. If a study is to be made in which the number of nodes involved is used as one of the criteria for treatment, the ordinary laboratory examination is useless, since most laboratories will dig out no more than 5 to 14 nodes per specimen.

These specimens can be cleared, and it is possible to get most of the nodes that are one to one-and-one-half low power field in diameter. This is done by placing the removed breast in either water or salt solution, spreading the tissue a little, and allowing it to remain in the solution for a day when the blood will be washed out; it is then fixed in formalin, dried with 50, 75, 95, and 100% alcohol, placed in cedar oil or oil of wintergreen, and the nodes removed. Four to 6 nodes can be placed in a single paraffin block and sectioned, and this will be a better guide as to what is actually happening.

Perhaps a high number of nodes was examined per specimen in this study, but I have a suspicion that this is not true, and if so, then any conclusion regarding the prognostic value of lymph node involvement is worthless.

Dr. Bernard Fisher (Closing): I should like to thank all of the participating institutions and their responsible investigators for making this study possible. They are all listed by name in the paper.

I certainly agree with Dr. Gilchrist's remarks and thank him for commenting. One of the by-products of a cooperative study such as this is the procurement of data concerning the biology of cancer. We are in the process of obtaining information relative to the number of positive nodes in all of the patients entered into the study. A preliminary examination of data has revealed that this may vary anywhere from zero number of nodes in a specimen to 80 or more. We plan to correlate these findings with what has happened to the patient.

Another bit of interesting information that has come to light concerns the relation of time of recurrence following operation to time of death. It does not seem to make any difference how soon following operation a recurrence is observed; the time from recurrence to death remains about the same whether recurrence occurs 1 year or 5 years after operation. Again, I should like to thank the contributing investigators who have made this possible.